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Dated: 4 May 2005 Signature: (Alicia R. Lewis)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (IPEA/US)

International Application No.	:	PCT/US2004/011812
International Filing Date	:	16 April 2004 (16.04.04)
Earliest Priority Date	:	16 April 2003 (16.04.03)
Applicant(s)	:	Celator Technologies, Inc.
Title	:	COMPOSITIONS FOR DELIVERY OF DRUG COMBINATIONS
IPC Number	:	A61K

RESPONSE TO FIRST WRITTEN OPINION

MS PCT
Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is a response to a Written Opinion issued by the International Searching Authority U.S. on 9 February 2005. A Chapter II Demand was filed in the present application on 21 October 2004. Thus, the present response, due within three months from the date of mailing of PCT/ISA/220, is timely. In response to the Written Opinion, Applicant's amend claims 1, 3, 8, 10, 11, 12, 13, 14, 22, 23 and 24. Applicants also submit replacement pages 72-77 for originally filed pages 72-77 to reflect the amendments to claims 1, 3, 8, 10, 11, 12, 13, 14, 22, 23 and 24. Clarifying amendments to claims 1 and 14 are offered and multiple dependencies have been scaled back. A copy of the claims showing the amendments made are also enclosed.

The Examiner refused to examine claims 4-13 and 22-24 as multiply dependent claims improperly dependent on a claim that is itself multiply dependent. This has been corrected in all cases. Therefore, consideration of these claims is requested.

Claim 1 has been amended to clarify that the delivery vehicles are particulate. This is supported by the definition of delivery vehicles in the specification on pages 15-16 in paragraph 69. As stated in the bridging sentence "The compositions thus contain delivery vehicles which are particulate in nature and contain the desired ratio of therapeutic agents."

Claim 14 has further been clarified to note that the administering is substantially simultaneous. Support for this limitation is found, for example, on page 39 in paragraph 141 and on page 8 in paragraph 22.

Claims 1 and 14 were said to lack novelty as anticipated by Nice, U.S. 5,547,940. The amendment to claims 1 and 14 is completely responsive to this rejection. No particulate delivery vehicles are disclosed in Nice. This is merely a clarifying amendment, as noted above.

But there are other reasons that this claim is not anticipated. As applicants are sure the Examiner is aware, each and every element of the claim must be met in order for anticipation to be found. Clearly, there is no teaching in Nice that the delivery vehicles in the first and the second compositions be coordinated with respect with pharmacokinetic behavior, nor is there any provision for instructions or amounts as set forth in the last paragraphs of claims 1 and 14 that the amounts directed to be administered or actually administered are in an non-antagonistic ratio. Thus, Nice clearly does not anticipate claims 1 and 14 either as filed or as amended. Example 17, cited in the Written Opinion, describes none of these limitations.

Claims 1-2, 14 and 21 were also considered to lack novelty as anticipated by Lam, U.S. 5,055,291.

First, although liposomes are described in Lam as possible carriers, this is not a requirement of the kits Lam describes at column 5, lines 51-65. The absolute requirement in all of the present claims, that the delivery vehicles be particulate, thus distinguishes the teaching of Lam where the use of liposomes is not a requirement, but merely an alternate possibility and for only one of the two components. As described in Lam, one of the components of the kit, at most, is permitted to be coupled to a particulate carrier. It appears that only the monoclonal antibodies associated with the cytotoxic component, which is encapsulated in liposomes, are coupled to particulate carriers (see column 4, lines 39-42). Thus, the kits of Lam do not inevitably include liposomes as carriers for even one of the components.

More clearly, there is no teaching in Lam that liposomes or any other type of carrier be coordinated with respect to pharmacokinetic behavior, nor is there any requirement that the first and second components be administered in non-antagonistic ratios. The disclosure of Lam has nothing to do with assuring maintenance of an appropriate ratio, but rather the non-cytotoxic agent is used to block certain sites from exposure to the cytotoxic agent.

Thus, clearly Lam fails to teach all of the elements of claims 1-2, 14 and 21.

Finally, all examined claims, claims 1-3 and 14-21 were said to lack inventive step in view of Vaage, *et al.* (*Int. J. Cancer* (1993) 54:959-964) either alone or in view of Lam. It is correct that Vaage reports the results of an experiment where vincristine and doxorubicin were each contained in liposomes and administered together to an *in vivo* tumor model. However, there is no mention of the requirement contained in independent claims 1 and 14 that the delivery vehicles in the first and second compositions be coordinated with respect to pharmacokinetic behavior. There is no evidence that such coordination was, in fact, established. Perhaps more important, the combined use of encapsulated vincristine and doxorubicin not only did not result in improved therapeutic effect, but vincristine inhibited the therapeutic efficacy of

the encapsulated doxorubicin (see page 962, right-hand column). Only when the injections of the encapsulated drugs were separated by three days was there any improvement in therapeutic effect. While inclusion in a kit does not itself require simultaneous administration, as does claim 14, there is little point in formulating a kit when the time separation of administration is so significantly long. Thus, Vaage would not lead one of ordinary skill to propose preparing a kit as required by claims 1-13, nor does it provide encouragement for simultaneous administration as required by claims 14-24. The suggestion of Lam to prepare a kit is simply not appropriate in view of the teachings of Vaage.

In summary, Nice does not anticipate either independent claim 1 or 14 because it does not describe particulate vehicles as carriers, it does not require that the carriers be coordinated with respect to pharmacokinetic behavior, and it is silent on administering at least two compositions in a non-antagonistic ratio.

Lam does not anticipate any claims as it merely suggests a particulate carrier for only one of the two compositions included in the kit and does not require even that much; it does not require coordination with respect to pharmacokinetic behavior, nor does it pertain to a treatment where behavior in a non-antagonistic way has any relevance. If anything, the two components in the Lam system are "antagonistic" as the non-cytotoxic agent is intended to block the target for the cytotoxic component.

Vaage does not suggest the invention as there is no teaching of coordinating the pharmacokinetics of the liposomes used in the compositions and it is clear that substantially simultaneous administration as required by claim 14 is disadvantageous in view of the results obtained. As non-antagonistic results are achieved only when the times of administration are widely separated, there is no suggestion that the compositions be included in a kit which would be useful, of course, only when administration times are proximal.

Thus, it is believed that all pending claims, claims 1-24 are patentable over the art.

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or to credit any overpayment to Deposit Account No. 03-1952.

Dated: 4 May 2005

Respectfully submitted,

By Kate H. Murashige

Kate H. Murashige
Registration No. 29,959
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125

Cc: International Bureau

1. A kit for treatment of a subject which kit comprises

in a first container a composition comprising particulate delivery vehicles stably associated with at least one first therapeutic agent;

in a second container a second composition comprising particulate delivery vehicles stably associated with at least a second therapeutic agent;

wherein the delivery vehicles in said first and second compositions are coordinated with respect to pharmacokinetic behavior; and

wherein said kit further contains instructions for administering said first and second composition at ratios of said first and second therapeutic agent that are non-antagonistic and/or wherein the amounts of said first and second compositions in said containers is proportional to a ratio of said first and second therapeutic agent that is non-antagonistic and/or said containers are calibrated to dispense amounts of said first and second composition wherein the ratio of first and second therapeutic agents is non-antagonistic.

2. The kit of claim 1, wherein the containers are syringes.

3. The kit of claim 1, wherein said agents are antineoplastic agents.

4. The kit of any of claims 1-3, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range where > 1% of relevant cells are affected ($f_a > 0.01$) in an *in vitro* assay for cytotoxicity.

5. The kit of claim 4, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected ($f_a = 0.1$-0.9) in said *in vitro* assay.

6. The kit of claim 5, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected ($f_a = 0.2$-0.8) in said *in vitro* assay.

7. The kit of claim 6, wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

Claims

8. The kit of any of claims 1-3, wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

9. The kit of claim 8, wherein said vehicles have a mean diameter of less than 250 nm.

10. The kit of any of claims 1-3, wherein said delivery vehicles comprise
liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

11. The kit of any of claims 1-3, wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

12. The kit of any of claims 1-3, wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

Claims

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

13. The kit of any of claims 1-3, wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

Claims

14. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of a first composition comprising particulate delivery vehicles stably associated with at least a first therapeutic agent and a second composition comprising particulate delivery vehicles stably associated with at least a second therapeutic agent, at substantially the same time,

wherein the delivery vehicles in said first and second composition are coordinated with respect to pharmacokinetics; and

wherein said administering is at a ratio of first therapeutic agent to second therapeutic agent that is non-antagonistic.

15. The method of claim 14, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1%-99% of the cells are affected (f_a = 0.01-0.99) in an *in vitro* assay for cytotoxicity or cytostasis.

16. The method of claim 15, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in an *in vitro* assay for cytotoxicity or cytostasis.

17. The method of claim 16, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in an *in vitro* assay for cytotoxicity or cytostasis.

18. The method of claim 17, wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in an *in vitro* assay for cytotoxicity or cytostasis.

19. The method of any of claims 14-18, wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

20. The method of any of claims 14-18, wherein said vehicles have a mean diameter of less than 250 nm.

Claims

21. The method of any of claims 14-18, wherein said delivery vehicles comprise
liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

22. The method of any of claims 14-18, wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

23. The method of any of claims 14-18, wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

Claims

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

24. The method of any of claims 14-18, wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

Amended Claims (changes shown)

1. A kit for treatment of a subject which kit comprises

in a first container a composition comprising particulate delivery vehicles stably associated with at least one first therapeutic agent;

in a second container a second composition comprising particulate delivery vehicles stably associated with at least a second therapeutic agent;

wherein the delivery vehicles in said first and second compositions are coordinated with respect to pharmacokinetic behavior; and

wherein said kit further contains instructions for administering said first and second composition at ratios of said first and second therapeutic agent that are non-antagonistic and/or wherein the amounts of said first and second compositions in said containers is proportional to a ratio of said first and second therapeutic agent that is non-antagonistic and/or said containers are calibrated to dispense amounts of said first and second composition wherein the ratio of first and second therapeutic agents is non-antagonistic.

2. The kit of claim 1, wherein the containers are syringes.

3. The kit of claim 1 ~~or 2~~, wherein said agents are antineoplastic agents.

4. The kit of any of claims 1-3, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range where > 1% of relevant cells are affected ($f_a > 0.01$) in an *in vitro* assay for cytotoxicity.

5. The kit of claim 4, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected ($f_a = 0.1$-0.9) in said *in vitro* assay.

6. The kit of claim 5, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected ($f_a = 0.2$-0.8) in said *in vitro* assay.

7. The kit of claim 6, wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

Amended Claims (changes shown)

8. The kit of any of ~~claims 1-7~~ claims 1-3, wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

9. The kit of claim 8, wherein said vehicles have a mean diameter of less than 250 nm.

10. The kit of any of ~~claims 1-9~~ claims 1-3, wherein said delivery vehicles comprise

liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

11. The kit of any of ~~claims 1-10~~ claims 1-3, wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

12. The kit of any of ~~claims 1-10~~ claims 1-3, wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

Amended Claims (changes shown)

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

13. The kit of any of ~~claims 1-10~~ claims 1-3, wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

Amended Claims (changes shown)

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

14. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of a first composition comprising particulate delivery vehicles stably associated with at least a first therapeutic agent and a second composition comprising particulate delivery vehicles stably associated with at least a second therapeutic agent, at substantially the same time,

wherein the delivery vehicles in said first and second composition are coordinated with respect to pharmacokinetics; and

wherein said administering is at a ratio of first therapeutic agent to second therapeutic agent that is non-antagonistic.

15. The method of claim 14, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1%-99% of the cells are affected (f_a = 0.01-0.99) in an *in vitro* assay for cytotoxicity or cytostasis.

16. The method of claim 15, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in an *in vitro* assay for cytotoxicity or cytostasis.

17. The method of claim 16, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in an *in vitro* assay for cytotoxicity or cytostasis.

18. The method of claim 17, wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in an *in vitro* assay for cytotoxicity or cytostasis.

19. The method of any of claims 14-18, wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

20. The method of any of claims 14-18, wherein said vehicles have a mean diameter of less than 250 nm.

Amended Claims (changes shown)

21. The method of any of claims 14-18, wherein said delivery vehicles comprise

liposomes, and/or

lipid micelles, and/or

block copolymer micelles, and/or

microparticles, and/or

nanoparticles, and/or

polymer lipid hybrid systems, and/or

derivatized single chain polymers.

22. The method of any of ~~claims 14-21~~ claims 14-18, wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

23. The method of any of ~~claims 14-21~~ claims 14-18, wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

Amended Claims (changes shown)

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

24. The method of any of ~~claims 14-21~~ claims 14-18, wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.